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The diagnostic value of non-invasive serum liver fibrosis indices in the prediction of portal hypertension in cirrhotic patients: a cross-sectional study

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Abstract

Introduction: Considering that portal hypertension is principally caused by hepatic fibrosis, some studies postulated the predictive value of serum liver fibrosis indices in the diagnosis of portal hypertension. In this study we assessed the prognostic value of serum indices in the diagnosis of portal hypertension in cirrhotic patients.

Methods: One hundred two cirrhotic patients were selected according to inclusion/exclusion criteria. Cirrhosis and the Child-Pugh score was determined by the gastroenterologist. Portal hypertension was diagnosed by the radiologist using the color Doppler method. The fasting blood sample was drawn and different serum indices were determined. The following indices were calculated: FIB4, Fibroindex, APRI, FORNS, LOK.

Results: The patients mean age was 54.39 ± 6.60 years. About 52.94% of the patients were women. The mean liver enzymes level was higher in patients with portal hypertension. In 50.98% of patients, the etiology of cirrhosis was viral hepatitis. Significant differences was observed between the two groups regarding the studied indices ($P < 0.05$). According to the results of the ROC curve, the FORNS index was a better predictive marker of portal hypertension in cirrhotic patients. The maximum AUC (area under the curve) was for the FORNS index. According to the results of diagnostic tests, the FORNS index had adequate sensitivity and specificity in the diagnosis of portal hypertension with the cut-off value of 8.51.

Conclusion: The results of the present study showed that the FORNS index is a better predictor of portal hypertension in cirrhotic patients.

Introduction

One of the important complications of liver cirrhosis is portal hypertension that can result in different complications such as ascites, esophageal varices, and hepatic encephalopathy. In addition, it can affect the prognosis and management of cirrhosis.[1-4] In this regard, Baveno VI Consensus Conference strongly suggested the screening of all cirrhotic patients for the presence of portal hypertension.[5]

The gold standard of assessing the portal hypertension is a hepatic venous pressure gradient (HVPG) which is an invasive method. Less invasive methods for the diagnosis of portal hypertension include Doppler ultrasound evaluation and transient elastography. However, these methods are expensive and available only in specialized centers with expert operators that limit their clinical application.

Recently, some laboratory and clinical indices have been developed as the noninvasive alternatives to HVPG.[6] Among these methods, serum markers are preferred due to their simplicity and accessibility. Considering that portal hypertension is principally caused by hepatic fibrosis, some studies postulated the predictive value of serum liver fibrosis indices in the diagnosis of portal hypertension.[2,7-9] However, they provided mixed results. So, in this study, we aimed to evaluate the diagnostic value of APRI, Fibroindex, FORNs, LOK, Fib-4, as a predictor of portal hypertension in patients with cirrhosis.

Materials and Methods

In the present cross-sectional study, 102 cirrhotic patients referred to Imam Reza hospital of Tabriz University of Medical Sciences, from October 2018 to April 2019 were studied. The patients were included if they aged 18-75

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years old and their Child-Pugh score were B or C. The exclusion criteria were as follows: getting treatment for portal hypertension, history of gastrointestinal bleeding, encephalopathy, moderate and severe ascites, liver cancer, pulmonary or renal complications of cirrhosis, portal vein thrombosis or being pregnant.

The sample size for the present study was calculated by MEDCALC© using the results of a previous study[9] and considering the 80% power and 95% confidence interval.

Cirrhosis was diagnosed by an expert gastroenterologist using histopathologic criteria and imaging signs. The severity of cirrhosis was determined using Child-Pugh score considering the laboratory and clinical parameters including serum bilirubin, albumin, and prothrombin time international normalized ratio (INR), encephalopathy, and ascites.

The portal hypertension was diagnosed using the color Doppler method by expert radiologist considering the following criteria: portal vein diameter, portal vein velocity, hepatic artery resistant index, and splenic artery resistant index.

For calculating serum liver fibrosis indices, 5 mL fasting blood sample was obtained and alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), gamma globulin, albumin, platelet, and INR were measured and following indices were calculated[10]:

APRI = (AST (IU/L)/AST (upper normal limit)/PLT (*10^9/L);

Fib4 = [age (years) * AST (IU/L)]/ [PLT (*10^9/L)] * [ALT (IU/L) 1/2].

LOK= 5.56 – 0.0089 × (platelet count) + 1.26 × (AST/ALT) + 5.27 × INR

FORNS=7.811 - 3.131 * ln (platelet count) + 0.781 * ln (GGT) + 3.467 * ln (age) - 0.014 * (cholesterol)

Fibroindex = 1.738 - 0.064 [PLT(*10^4/mm³)] + 0.005 [AST (U/L)] + 0.463 [G (g/dL)].

Statistical analysis

IBM SPSS version 21 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Kolmogorov-Smirnov test was used for assessing the data normality. Considering the normal distribution of data, continuous variables were presented as mean and SD and categorical variables as frequency and percent. An independent t test was used for between-group comparisons. Receiver operating characteristic (ROC) curve analysis was used for assessing the performance of indices for diagnosis of portal hypertension and area under the curve (AUC), sensitivity and specificity were calculated. P value <0.05 was considered significant.

Results

Totally, 102 cirrhotic patients (48 men and 54 women) with the mean age of 54.39 ± 6.60 were included in the present study. The demographic and clinical characteristics of

patients are presented in Table 1. The etiology of cirrhosis in 50.98% of patients was viral and 71.56% of patients were classified as a Child-Pugh score of B. Moreover, 59.80% of patients had portal hypertension.

Table 2 presents the comparison of the mean score of liver fibrosis indices according to portal hypertension status. According to the results of the independent t test, the mean score of studied indices were significantly higher in patients with portal hypertension compared with those without portal hypertension.

Subgroup analysis was also performed to compare the mean score of serum fibrosis indices according to cirrhosis etiology and severity. The results indicated that there were no significant differences in the mean score of indices among different etiologies (viral and non-viral) and different Child-Pugh classes (Table 3).

The performance of different serum liver fibrosis indices in the detection of portal hypertension in cirrhotic patients is depicted in Figure 1 and the best cut-off value, sensitivity, and specificity of indices are presented in

Table 1. The demographic and clinical characteristics of patients

Variables	Total (n=102)	Patients with portal hypertension (n=61)	Patients without portal hypertension (n=41)
Age (years)	54.39 ± 6.60	54.56 ± 5.56	54.27 ± 7.10
Sex (male/female)	48/54	28/33	20/21
Gama globulin (g/dL)	1.65 ± 0.38	1.72 ± 0.41	1.63 ± 0.85
ALT (IU/L)	39.63 ± 38.17	45.92 ± 44.15	33.52 ± 31.95
AST (IU/L)	46.09 ± 46.64	50.34 ± 49.71	42.62 ± 41.64
GGT (IU/L)	66.61 ± 58.85	68.16 ± 67.46	64.25 ± 73.64
Platelet	107.61 ± 67.85	99.17 ± 62.86	117.95 ± 86.75
INR	1.26 ± 0.29	1.29 ± 0.19	1.24 ± 0.31
Cholesterol	147.33 ± 48.33	146.58 ± 46.11	148.21 ± 52.17
Etiology			
Viral	52 (50.98)	33 (54.09)	19 (46.34)
Non-viral	50 (49.01)	28 (45.90)	22 (53.66)
Child-Pugh class			
B	73 (71.56)	38 (62.29)	35 (85.36)
C	29 (28.43)	23 (37.70)	6 (14.63)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; INR: International normalized ration

Table 2. The mean score of liver fibrosis scores stratified by portal hypertension status

Indices	Patients with portal hypertension	Patients without portal hypertension	P value *
FIB-4	4.12 ± 0.70	3.85 ± 0.38	0.02
APRI	1.21 ± 0.14	1.01 ± 0.22	0.001
Fibroindex	10.21 ± 3.72	8.36 ± 2.44	0.003
FORNS index	8.66 ± 0.49	8.07 ± 0.63	0.001
Lok index	0.82 ± 0.18	0.73 ± 0.15	0.001

FIB-4: Fibrosis-4; APRI: AST to Platelet Ratio Index.
*Independent t test.

Table 3. The mean liver fibrosis scores stratified by cirrhosis etiology and severity

Indices	Viral	Non-viral	P value*	Child-Pugh B	Child -Pugh C	P value*
FIB-4	4.04±0.41	3.97±0.75	0.53	4.07±0.47	3.84±0.85	0.23
APRI	1.15±0.23	1.12±0.25	0.46	1.11±0.68	1.18±0.25	0.11
Fibroindex	9.59±3.44	9.35±3.35	0.72	9.55±3.51	9.34±2.88	0.68
FORNS index	8.54±0.57	8.31±0.65	0.06	8.36±0.62	8.60±0.63	0.06
Lok index	0.79±0.08	0.78±0.08	0.91	0.78±0.08	0.79±0.09	0.50

FIB-4: Fibrosis-4; APRI: AST to platelet ratio index.
*Independent t test.

Table 4. Performance of liver fibrosis indices for predicting portal hypertension

Indices	Cut-off	AUC	P value	Sensitivity (%)	Specificity (%)
FIB-4	4.32	0.77	<0.001	73.31	87.71
APRI	1.14	0.73	<0.001	83.60	67.30
Fibroindex	11.28	0.63	0.02	45.25	92.68
FORNS index	8.51	0.86	<0.001	91.11	90.20
Lok Index	0.8	0.80	<0.001	98.31	47.31

FIB-4: Fibrosis-4; APRI: AST to platelet ratio index; AUC: Area under the curve.

Table 4. As can be seen, FORNS and LOK indices had the best performance by AUC of 0.86 and 0.80, respectively. In addition, FORNS index >8.51 had a sensitivity of 91.11% and specificity of 90.2% for the detection of portal hypertension in cirrhotic patients which are higher than those of FIB-4, APRI, Fibroindex, and LOK.

Discussion

Portal hypertension is the main reason for cirrhosis complications and affects disease prognosis. Although HVPG and color Doppler methods perform well in the diagnosis of portal hypertension, they are invasive and require an expert to perform them. So, we aimed to assess the diagnostic performance of non-invasive serum indices for identification of portal hypertension in cirrhotic patients in the present study.

The results indicated that the FORNS index had higher sensitivity and specificity compared with other studied indices. Previous studies in patients with cirrhosis also showed that the FORNS index was better than other indices to predict esophageal varices and portal hypertension. Sebastiani et al in 510 cirrhotic patients showed that LOK and FORNS indices could predict esophageal varices better than other indices.[6] In another study, Rizqi et al also showed that FORNS index with the sensitivity of 63.9% and specificity of 73.3% could predict esophageal varices in cirrhotic patients.[11]

However, the results of our study were contrasted with other studies conducted in this regard. In a multicenter study, Zhang et al[9] studied the predictive value of different indices for diagnosis of portal hypertension and showed that liver stiffness measurement could predict portal hypertension better than serum liver fibrosis indices in cirrhotic patients. However, LOK and FORNS indices were not used in the mentioned study. In another study, Cho et al showed that liver stiffness measurement could better predict portal hypertension in alcoholic liver cirrhosis.[8] Considering that this study was conducted only in patients with alcoholic liver cirrhosis, the generalizability of the results is limited. In another recent study, Wang et al showed that the LOK index could predict portal hypertension better than other serum liver fibrosis indices in cirrhotic patients. But they concluded that since all studied indices had AUC<0.8, they could not be considered as accurate indices for prediction of portal hypertension.[7] In line with these results, we also showed that all indices had AUC ≤0.8 except the FORNS index. This may be due to this fact that all these indices were initially developed for the prediction of liver fibrosis in cirrhotic patients with hepatitis C.[12] However, we included cirrhotic patients with various etiology in the present study, intending to compare the mean score of different indices in patients with different etiology and disease severity. We could not find significant differences between groups which might be due to the limited number of patients in each group.
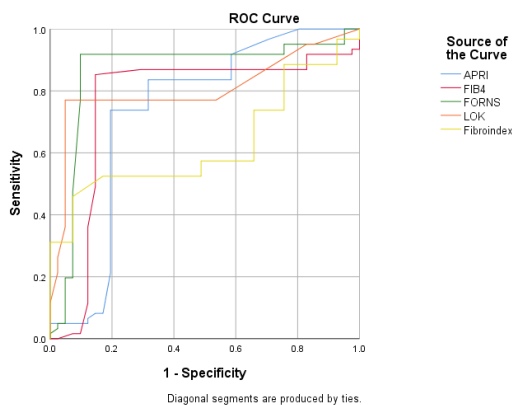

Figure 1. ROC curve of liver fibrosis indices in predicting portal hypertension.
FIB-4: Fibrosis-4; APRI: AST to Platelet Ratio Index.

Study Highlights

What is current knowledge?

- The gold standard of assessing the portal hypertension is a hepatic venous pressure gradient (HVPG) which is an invasive method.
- Some laboratory and clinical indices have been developed as the noninvasive alternatives to HVPG.
- Considering that portal hypertension is principally caused by hepatic fibrosis, it is postulated the predictive value of serum liver fibrosis indices in the diagnosis of portal hypertension

What is new here?

- The mean liver enzymes level was higher in patients with portal hypertension.
- The FORNS index was a better predictor of portal hypertension in cirrhotic patients.
- The FORNS index had adequate sensitivity and specificity in the diagnosis of portal hypertension with the cut-off value of 8.51.

Moreover, portal hypertension was not developed only due to the liver fibrosis.[13] Thus, using only liver fibrosis indices could not accurately predict portal hypertension in cirrhotic patients.

The present study had some limitations. The sample size was limited. Moreover, we used color Doppler for measuring portal hypertension. Although previous studies showed high sensitivity and specificity of this method for diagnosis of portal hypertension,[14] HVPG is a more accurate method and considered as a gold standard. Future studies should be conducted with a larger sample size especially in the different etiologic groups and use a more accurate method for diagnosis of portal hypertension.

Conclusion

In conclusion, the results of the present study showed that the FORNS index could predict portal hypertension in cirrhotic patients with different etiology better than other indices.

Conflict of Interest

None.

Ethical Approval

All patients gave written informed consent and the study was approved by the ethics committee of Tabriz University of medical sciences, Tabriz, Iran (Ethics code: IR.TBZMED.REC.1397.1089).

Author's contributions

MFD, MKT and MHS contributed to the conception and design of the study. SA, AR and LA contributed to acquisition of data. ZN and SA contributed to data analysis and MFD, MHS, MKT contributed to the data interpretation. ZN and SA drafted the first version of the manuscript and all other authors critically revised it. Finally, all authors approved the final version of the manuscript.

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